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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,872	09/05/2003	James E. Bear	0492611-0512 (MIT9984)	7189

24280 7590 08/08/2007

CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

EXAMINER	
MAKAR, KIMBERLY A	
ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
08/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/655,872	BEAR ET AL.	
	Examiner	Art Unit	
	Kimberly A. Makar, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2003*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-124* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-38, and 58-60, and 124 drawn to a lentiviral vector comprising the following elements: a nucleic acid whose sequence includes (i) a functional packaging signal; (ii) a multiple cloning site; and (iii) at least one additional element selected from the group consisting of: a second MCS, a second MCS into which a heterologous nucleic acid is inserted, an HIV FLAP element, an expression –enhancing posttranscriptional regulatory element, a target site for a site-specific recombinase, and a self-inactivating LTR, wherein the lentiviral vector is a lentiviral transfer plasmid or an infections lentiviral particle, a cell encompassing the transfer or provirus of the lentiviral vector, and kit comprising the lentiviral transfer plasmid classified in class 424, subclass 93.1.

II. Claims 39-40, 42 drawn to a lentiviral vector comprising an RNA polymerasé III promoter that is a U6 promoter, classified in class 514, subclass 44.

III. Claims 39, 41-42, drawn to a lentiviral vector comprising an RNA polymerase III promoter that is an HI promoter, classified in class 514, subclass 44.

IV. Claims 43, 47, 51, drawn to a lentiviral vector having a sequence, or a sequence that differs by not more than 99 to 100 nucleotides, from SEQ ID NOS: 2, 3, 4, 5, 6, 7, 8, or 9, classified in class 514, subclass 44.

V. Claims 44-46, 48-50, 52, 53, 55, drawn to a collection of at least two vectors having a sequence, or a sequence that differs by not more than 99 to 100 nucleotides, from SEQ ID NOS: 2, 3, 4, 5, 6, 7, 8, or 9, classified in class 514, subclass 44.

VI. Claims 56-57, and 124 drawn to a three or four plasmid lentiviral expression system comprising: (a) a first plasmid whose sequence comprises a nucleic acid sequence of at least a part of a lentiviral genome, wherein the plasmid (i) contains at least one defect in at least one gene encoding a lentiviral structural protein, and (ii) lacks a functional packaging signal; (b) a second plasmid whose sequences comprises a nucleic acid sequence of a virus, wherein the plasmid (i) expresses a viral envelope protein and (ii) lacks a functional packaging signal; and (c) a third plasmid whose nucleic acid sequence includes (i) a functional packaging signal (ii) a multiple cloning site, and (iii) at least one additional element selected from the groups consisting of: a second MCS, a second MCS into which a heterologous nucleic acid is inserted; an HIV FLAP element, and expression enhancing posttranscriptional regulatory element, a target site for a site-specific recombinase, and an self-

inactivating LTR, and kit comprising a lentiviral transfer plasmid classified in class 435, subclass 466.

VII. Claims 61-62, 70-73, drawn to a transgenic animal whose cells contain the lentiviral vector of claim 1, and methods of making the transgenic, classified in class 800, subclass 3.

VIII. Claim 63, drawn to a method of making a producer cell line comprising introducing the lentiviral vector of claim 1 into a host cell, wherein the lentiviral vector is a transfer plasmid, and introducing a packaging plasmid and an envelope plasmid into the host cell, classified in class 435, subclass 455.

IX. Claims 64-65, drawn to a method of producing lentiviral particles by introducing the lentiviral vector of claim 1 into a helper cell that expresses protein required for production of infectious lentiviral particles, classified in class 435, subclass 235.1.

X. Claims 66, drawn to a method of expressing a heterologous nucleic acid in a target cell comprising introducing a lentiviral vector of claim 1 into the target cell, wherein the lentiviral vector comprises a heterologous nucleic acid operably linked to a promoter, and expressing the heterologous nucleic acid therein, classified in class 435, subclass 91.1.

XI. Claims 67-69, 71-73 drawn to a method for achieving controlled expression of a heterologous nucleic acid in a cell comprising the steps of: (i) providing a modified lentiviral vector comprising a heterologous nucleic

acid inserted between sites for recombinant; (ii) introducing the modified lentiviral vector into the cell; and (iii) subsequently inducing expression of the recombinant in the cell, thereby preventing expression of the heterologous nucleic acid within the cell, classified in class 435, subclass 91.4.

XII. Claims 74-79, 81-92, drawn to a lentiviral vector whose presence within a cell results in transcription of one or more ribonucleic acids that self-hybridize or hybridize to each other to form a short hairpin RNA or short interfering RNA that inhibits expression of at least one target transcript in the cell, wherein the lentiviral vector is a lentiviral transfer plasmid, and pharmaceutical compositions comprising the lentiviral vector classified in class 435, subclass 466.

XIII. Claims 74-78, 80-92, drawn to a lentiviral vector whose presence within a cell results in transcription of one or more ribonucleic acids that self-hybridize or hybridize to each other to form a short hairpin RNA or short interfering RNA that inhibits expression of at least one target transcript in the cell, wherein the lentiviral vector is an infectious lentiviral particle and a pharmaceutical composition comprising the infectious lentiviral particle, classified in class 435, subclass 70.1.

XIV. Claims 93-94, drawn to a three or four plasmid lentiviral expression system comprising (i) a lentiviral transfer plasmid comprising a heterologous nucleic acid operably linked to a promoter, so that

transcription of the heterologous nucleic acid produces one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA targeted to a target transcript; (ii) a packaging plasmid and (iii) and Env-encoding plasmid, classified in class 435, subclass 489.

XV. Claims 95-103, 105, drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral transfer plasmid, classified in class 435, subclass 471.

XVI. Claims 95-102, 104-105, drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral particle, classified in class 435, subclass 455.

XVII. Claims 106-109, and 111, drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby

preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid, classified in class 435, subclass 471.

XVIII. Claims 106-108, 110-111, drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral particle, classified in class 435, subclass 455.

XIX. Claims 112-114, 116, drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for

transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid, classified in class 514, subclass 44.

XX. Claims 112-113, 115-116, drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral particle, classified in class 424, subclass 93.1.

XXI. Claims 117-118, drawn to a method of treating or preventing infection by an infectious agent, the method comprising the steps of: administering to a subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising an effective amount of a

lentiviral vector, wherein presence of the lentiviral vector in a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that is targeting to a transcript produced during infection by the infectious agent, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspect of infection by or replication of the infectious agent, classified in class 800, subclass 21.

XXII. Claims 119-123, drawn to a method of treating or preventing a disease or clinical condition, the method comprising: removing a population of cells from a subject at risk of or suffering from a disease or clinical condition; engineering or manipulating the cells to contain an effective amount of siRNA or shRNA targeted to a transcript, which transcript is characterized in that its degradation delays, prevents or inhibits one or more aspects of the disease or clinical condition, and returning at least a portion of the cells to the subject, classified in class 424, subclass 93.1.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I, II, III, IV, XII, and XIII are all directed towards distinct individual lentiviral compositions:

3. Inventions I and II are directed to related lentiviral vectors. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the

inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed are materially different in design, do not overlap in scope, and are not obvious variants. Invention I, is drawn to a lentiviral vector comprising the following elements: a nucleic acid whose sequence includes (i) a functional packaging signal; (ii) a multiple cloning site; and (iii) at least one additional element selected from the group consisting of: a second MCS, a second MCS into which a heterologous nucleic acid is inserted, an HIV FLAP element, an expression –enhancing posttranscriptional regulatory element, a target site for a site-specific recombinase, and a self-inactivating LTR, wherein the lentiviral vector is a lentiviral transfer plasmid or an infections lentiviral particle, and a cell encompassing the transfer or provirus of the lentiviral vector, whereas invention II is drawn to a lentiviral vector comprising an RNA polymerase III promoter that is a U6 promoter. The lentiviral vectors of group II do not require the structural limitations of invention I (MCS, HIV FLAP, etc) and would only function in cells comprising a pol III protein, therefore they would not function in the same way as the lentiviral vectors of invention I. The lentiviral vectors of invention I do not require the use of a heterologous promoter sequence, therefore the heterologous nucleic acids would only be driven in cells lentiviral vectors are capable of expressing in. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

4. Inventions I and III are directed to related lentiviral vectors. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use

together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed are materially different in design, do not overlap in scope, and are not obvious variants. Invention I, is drawn to a lentiviral vector comprising the following elements: a nucleic acid whose sequence includes (i) a functional packaging signal; (ii) a multiple cloning site; and (iii) at least one additional element selected from the group consisting of: a second MCS, a second MCS into which a heterologous nucleic acid is inserted, an HIV FLAP element, an expression – enhancing posttranscriptional regulatory element, a target site for a site-specific recombinase, and a self-inactivating LTR, wherein the lentiviral vector is a lentiviral transfer plasmid or an infections lentiviral particle, and a cell encompassing the transfer or provirus of the lentiviral vector, whereas invention III is drawn to a lentiviral vector comprising an RNA polymerase III promoter that is a HI promoter. The lentiviral vectors of invention III do not require the structural limitations of invention I (MCS, HIV FLAP, etc) and would only function in cells comprising a pol III protein, therefore they would not function in the same way as the lentiviral vectors of invention I. The lentiviral vectors of invention I do not require the use of a heterologous promoter sequence, therefore the heterologous nucleic acids would only be driven in cells lentiviral vectors are capable of expressing in. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

5. Inventions I and IV are directed to related lentiviral vectors. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed are materially different in design, do not overlap in scope, and are not obvious variants. Invention I, is drawn to a lentiviral vector comprising the following elements: a nucleic acid whose sequence includes (i) a functional packaging signal; (ii) a multiple cloning site; and (iii) at least one additional element selected from the group consisting of: a second MCS, a second MCS into which a heterologous nucleic acid is inserted, an HIV FLAP element, an expression – enhancing posttranscriptional regulatory element, a target site for a site-specific recombinase, and a self-inactivating LTR, wherein the lentiviral vector is a lentiviral transfer plasmid or an infections lentiviral particle, and a cell encompassing the transfer or provirus of the lentiviral vector, whereas invention IV is drawn to a lentiviral vector having a sequence, or a sequence that differs by not more than 99 to 100 nucleotides, from SEQ ID NOS: 2, 3, 4, 5, 6, 7, 8, or 9. The lentiviral vectors of invention I do not require the sequence limitations of invention IV. The lentiviral vectors of invention IV do not require the structural limitations of invention I. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

6. Inventions I and XII are directed to related lentiviral vectors. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed are materially different in design, do not overlap in scope, and are not obvious variants. Invention I, is drawn to a lentiviral vector comprising the following elements: a nucleic acid whose sequence includes (i) a functional packaging signal; (ii) a multiple cloning site; and (iii) at least one additional element selected from the group consisting of: a second MCS, a second MCS into which a heterologous nucleic acid is inserted, an HIV FLAP element, an expression – enhancing posttranscriptional regulatory element, a target site for a site-specific recombinase, and a self-inactivating LTR, wherein the lentiviral vector is a lentiviral transfer plasmid or an infections lentiviral particle, and a cell encompassing the transfer or provirus of the lentiviral vector, whereas invention XII is drawn to a lentiviral vector whose presence within a cell results in transcription of one or more ribonucleic acids that self-hybridize or hybridize to each other to form a short hairpin RNA or short interfering RNA that inhibits expression of at least one target transcript in the cell, wherein the lentiviral vector is a lentiviral transfer plasmid, and pharmaceutical compositions comprising the lentiviral vector. The lentiviral vectors of invention I do not require the structural hybridization limitations of invention XII. The lentiviral vectors of invention XII do not require the structural limitations of invention I (MCS, HIV FLAP,

etc). Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

7. Inventions I and XIII are directed to related lentiviral vectors. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed are materially different in design, do not overlap in scope, and are not obvious variants. Invention I, is drawn to a lentiviral vector comprising the following elements: a nucleic acid whose sequence includes (i) a functional packaging signal; (ii) a multiple cloning site; and (iii) at least one additional element selected from the group consisting of: a second MCS, a second MCS into which a heterologous nucleic acid is inserted, an HIV FLAP element, an expression – enhancing posttranscriptional regulatory element, a target site for a site-specific recombinase, and a self-inactivating LTR, wherein the lentiviral vector is a lentiviral transfer plasmid or an infections lentiviral particle, and a cell encompassing the transfer or provirus of the lentiviral vector, whereas invention XIII is drawn to a lentiviral vector whose presence within a cell results in transcription of one or more ribonucleic acids that self-hybridize or hybridize to each other to form a short hairpin RNA or short interfering RNA that inhibits expression of at least one target transcript in the cell, wherein the lentiviral vector is an infectious lentiviral particle and a pharmaceutical composition comprising the infectious lentiviral particle. The lentiviral vectors of

invention I do not require the structural hybridization limitations of invention XIII. The lentiviral vectors of invention XIII do not require the structural limitations of invention I (MCS, HIV FLAP, etc). Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

8. Inventions II and III are directed to related inventions. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design and mode of operation and are mutually exclusive. Invention II is drawn to a lentiviral vector comprising an RNA polymerase III promoter that is a U6 promoter and invention III is drawn to a lentiviral vector comprising an RNA polymerase III promoter that is an HI promoter. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

9. Inventions II and IV are directed to related inventions. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design and mode of operation and do

not overlap in scope. Invention II is drawn to a lentiviral vector comprising an RNA polymerase III promoter that is a U6 promoter and invention IV is drawn to a lentiviral vector having a sequence, or a sequence that differs by not more than 99 to 100 nucleotides, from SEQ ID NOS: 2, 3, 4, 5, 6, 7, 8, or 9. The lentiviral vectors of invention IV do not require the pol III promoter of invention II, and the lentiviral vectors of invention II do not have the sequence restrictions of invention IV. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

10. Inventions II and XII are directed to related inventions. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design and mode of operation and do not overlap in scope. Invention II is drawn to a lentiviral vector comprising an RNA polymerase III promoter that is a U6 promoter and invention XII is drawn to a lentiviral vector whose presence within a cell results in transcription of one or more ribonucleic acids that self-hybridize or hybridize to each other to form a short hairpin RNA or short interfering RNA that inhibits expression of at least one target transcript in the cell, wherein the lentiviral vector is a lentiviral transfer plasmid, and pharmaceutical compositions comprising the lentiviral vector. The lentiviral transfer plasmids of invention XII do not require the pol III promoter of invention II, and the lentiviral vectors

of invention II do not have the structural hybridization limitations of the lentiviral transfer plasmids of invention XII. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

11. Inventions II and XIII are directed to related inventions. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design and mode of operation and do not overlap in scope. Invention II is drawn to a lentiviral vector comprising an RNA polymerase III promoter that is a U6 promoter and invention XIII is drawn to a lentiviral vector whose presence within a cell results in transcription of one or more ribonucleic acids that self-hybridize or hybridize to each other to form a short hairpin RNA or short interfering RNA that inhibits expression of at least one target transcript in the cell, wherein the lentiviral vector is an infectious lentiviral particle and a pharmaceutical composition comprising the infectious lentiviral particle. The infectious lentiviral particles of invention XIII do not require the pol III promoter of invention II, and the lentiviral vectors of invention II do not have the structural hybridization limitations of the lentiviral particles of invention XII. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

12. Inventions III and IV are directed to related inventions. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed differ in design and do not overlap in scope. Invention III drawn to a lentiviral vector comprising an RNA polymerase III promoter that is an HI promoter, is distinct from invention IV drawn to a lentiviral vector having a sequence, or a sequence that differs by not more than 99 to 100 nucleotides, from SEQ ID NOS: 2, 3, 4, 5, 6, 7, 8, or 9. The lentiviral vectors of invention III do not have the sequence limitations of invention IV, and the lentiviral vectors of invention IV do not have the structural requirements of invention III. The lentiviral vectors of invention III could have nucleic acid sequences more than 100 base pair different that those of invention IV, and the lentiviral vectors of invention IV do not necessarily have to have a pol III promoter element. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

13. Inventions III and XII are directed to related inventions. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed differ in design and do not overlap in scope. Invention III drawn

to a lentiviral vector comprising an RNA polymerase III promoter that is an HI promoter, is distinct from invention XII drawn to a lentiviral vector whose presence within a cell results in transcription of one or more ribonucleic acids that self-hybridize or hybridize to each other to form a short hairpin RNA or short interfering RNA that inhibits expression of at least one target transcript in the cell, wherein the lentiviral vector is a lentiviral transfer plasmid, and pharmaceutical compositions comprising the lentiviral vector. The lentiviral vectors of invention III do not have the structural hybridization limitations of the lentiviral vectors of invention XII, and the lentiviral vectors of invention XII do not have the structural requirements of a pol III promoter of invention III. The lentiviral vectors of invention XII do not necessarily have to have a HI pol III promoter element. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

14. Inventions III and XIII are directed to related inventions. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed differ in design and do not overlap in scope. Invention III drawn to a lentiviral vector comprising an RNA polymerase III promoter that is an HI promoter, is distinct from invention XIII drawn to a lentiviral vector whose presence within a cell results in transcription of one or more ribonucleic acids that self-hybridize or hybridize to each other to form a short hairpin RNA or short interfering RNA that inhibits expression

of at least one target transcript in the cell, wherein the lentiviral vector is an infectious lentiviral particle and a pharmaceutical composition comprising the infectious lentiviral particle. The lentiviral vectors of invention III do not have the structural hybridization limitations of the lentiviral particles of invention XIII, and the lentiviral vectors of invention XIII do not have the structural requirements of a pol III promoter of invention III. The lentiviral vectors of invention XIII do not necessarily have to have a HI pol III promoter element. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

15. Inventions XII and XIII are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because Invention XII is drawn to a lentiviral vector whose presence within a cell results in transcription of one or more ribonucleic acids that self-hybridize or hybridize to each other to form a short hairpin RNA or short interfering RNA that inhibits expression of at least one target transcript in the cell, wherein the lentiviral vector is a *lentiviral transfer plasmid*, and pharmaceutical compositions comprising the lentiviral vector is distinct from invention XIII drawn to a lentiviral vector whose presence within a cell results in transcription of one or more ribonucleic acids that self-hybridize or hybridize to each other to form a

short hairpin RNA or short interfering RNA that inhibits expression of at least one target transcript in the cell, wherein the lentiviral vector is *an infectious lentiviral particle* and a pharmaceutical composition comprising the infectious lentiviral particle. The lentiviral transfer plasmids of invention XII do not have the physical compositions of the lentiviral particles of invention XIII. The subcombination has separate utility such as the lentiviral transfer plasmid can be used in a probe in an immunoblot, or can be transfected into a cell without being incorporated into an infectious lentiviral particle.

16. The examiner has required restriction between combination and subcombination inventions. Where applicant elects a subcombination, and claims thereto are subsequently found allowable, any claim(s) depending from or otherwise requiring all the limitations of the allowable subcombination will be examined for patentability in accordance with 37 CFR 1.104. See MPEP § 821.04(a). Applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

17. Inventions V, VI and XIV are all directed towards distinct collections or libraries of lentiviral compositions or viruses:

18. Inventions V and VI are directed to related inventions. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as

claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design and do not overlap in scope. Invention V is drawn to a collection of at least two vectors having a sequence, or a sequence that differs by not more than 99 to 100 nucleotides, from SEQ ID NOS: 2, 3, 4, 5, 6, 7, 8, or 9, and invention VI is drawn to a three or four plasmid lentiviral expression system. The collection of vectors of invention V do not have to be used in a 3-4 vector expression system, and could be used as probes in an immunoblot. The expression system of invention VI does not require the vectors of invention V. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

19. Inventions V and XIV are directed to related inventions. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design and do not overlap in scope. Invention V is drawn to a collection of at least two vectors having a sequence, or a sequence that differs by not more than 99 to 100 nucleotides, from SEQ ID NOS: 2, 3, 4, 5, 6, 7, 8, or 9, and invention XIV is drawn to a three or four plasmid lentiviral expression system comprising (i) a lentiviral transfer plasmid comprising a heterologous nucleic acid operably linked to a promoter, so that transcription of the heterologous nucleic acid produces one or more RNAs that self-hybridize or hybridize with each other

to form an shRNA or siRNA targeted to a target transcript; (ii) a packaging plasmid and (iii) and Env-encoding plasmid),. The collection of vectors of invention V do not have to be used in a 3-4 vector expression system nor have the structural hybridization limitations of the vectors of invention XIV, and could be used as probes in an immunoblot. The expression system of invention XIV does not require the vectors of invention V. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

20. Inventions IV and XIV are directed to related inventions. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design and do not overlap in scope. Invention IV is drawn to is drawn to a three or four plasmid lentiviral expression system and invention XIV is drawn to a three or four plasmid lentiviral expression system comprising (i) a lentiviral transfer plasmid comprising a heterologous nucleic acid operably linked to a promoter, so that transcription of the heterologous nucleic acid produces one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA targeted to a target transcript; (ii) a packaging plasmid and (iii) and Env-encoding plasmid),. The collection of vectors of invention IV do not have the structural hybridization limitations of the vectors of invention XIV, and do not necessarily form such structures. The expression system of invention XIV does not require the

expression system of invention IV. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants

21. Inventions VIII, IX, X, XI, XV, XVI, XVII, XVIII, XIX, XX, XXI and XXII are all directed towards distinct methodologies using lentiviral vectors.

22. Inventions VIII and IX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention VIII, drawn to a method of making a producer cell line comprising introducing the lentiviral vector of claim 1 into a host cell, wherein the lentiviral vector is a transfer plasmid, and introducing a packaging plasmid and an envelope plasmid into the host cell, is distinct from invention IX drawn to a method of producing lentiviral particles by introducing the lentiviral vector of claim 1 into a helper cell that expresses protein required for production of infectious lentiviral particles. The method of making a stable cell line of invention VIII requires different processes and reagents than those used in the methodology of invention IX. Additionally, producing a stable cell line comprising the vectors of claim 1 does not require that the methodology produce viruses – the stable cell line could be used to amplify the nucleic acid vectors of claim 1 for other methodologies. Furthermore, the inventions as claimed do not

encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

23. Inventions VIII and X are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention VIII, drawn to a method of making a producer cell line comprising introducing the lentiviral vector of claim 1 into a host cell, wherein the lentiviral vector is a transfer plasmid, and introducing a packaging plasmid and an envelope plasmid into the host cell, is distinct from invention X, drawn to a method of expressing a heterologous nucleic acid in a target cell comprising introducing a lentiviral vector of claim 1 into the target cell, wherein the lentiviral vector comprises a heterologous nucleic acid operably linked to a promoter, and expressing the heterologous nucleic acid therein. The methodology of producing a stable cell line as that of invention VIII requires different steps and reagents (such as cell selection with antibiotics) than the methodology of invention X, which is the expression of the nucleic acids vectors of claim 1 in a target. The target cell of invention X could be a transient transfection into a bacterial cell for the propagation of the nucleic acid, and does not require the additional plasmids of invention VIII. Furthermore, the inventions as claimed

do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

24. Inventions VIII and XI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention VIII, drawn to a method of making a producer cell line comprising introducing the lentiviral vector of claim 1 into a host cell, wherein the lentiviral vector is a transfer plasmid, and introducing a packaging plasmid and an envelope plasmid into the host cell, is distinct from invention XI drawn to a method for achieving controlled expression of a heterologous nucleic acid in a cell comprising the steps of: (i) providing a modified lentiviral vector comprising a heterologous nucleic acid inserted between sites for recombinant; (ii) introducing the modified lentiviral vector into the cell; and (iii) subsequently inducing expression of the recombinant in the cell, thereby preventing expression of the heterologous nucleic acid within the cell. The methodology of producing a stable cell line as that of invention VIII requires different steps and reagents (such as cell selection with antibiotics) than the methodology of invention XI, which is achieving the controlled expression of the nucleic acids vectors of claim 1 in a target via recombination. The stable cell of invention VIII also requires additional plasmids for expression of the lentiviral vector. Furthermore, the inventions as

claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

25. Inventions VIII and XV are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention VIII, drawn to a method of making a producer cell line comprising introducing the lentiviral vector of claim 1 into a host cell, wherein the lentiviral vector is a transfer plasmid, and introducing a packaging plasmid and an envelope plasmid into the host cell, is distinct from invention XV drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral transfer plasmid. The methodologies require the use of distinct lentiviral vectors (those from claim 1 versus those from claim 74), and the methodology of producing a stable cell line, such as that in invention VIII requires distinct steps and reagents and effect than those of invention XV, whose expression of the vector results in an inhibition of a target transcript. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

26. Inventions VIII and XVI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use

together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention VIII, drawn to a method of making a producer cell line comprising introducing the lentiviral vector of claim 1 into a host cell, wherein the lentiviral vector is a transfer plasmid, and introducing a packaging plasmid and an envelope plasmid into the host cell, is distinct from invention XVI drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral particle. The methodologies require the use of distinct lentiviral vectors (those from claim 1 versus those from claim 74), and the methodology of producing a stable cell line, such as that in invention VIII requires distinct steps and reagents and effect than those of invention XVI, whose expression of the vector results in an inhibition of a target transcript. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

27. Inventions VIII and XVII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect

and do not overlap in scope. Invention VIII, drawn to a method of making a producer cell line comprising introducing the lentiviral vector of claim 1 into a host cell, wherein the lentiviral vector is a transfer plasmid, and introducing a packaging plasmid and an envelope plasmid into the host cell, is distinct from invention XVII drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid. The methodologies require the use of distinct lentiviral vectors, and the methodology of producing a stable cell line, such as that in invention VII requires distinct steps and reagents and effect (such as cell selection via a selectable marker and host cell propagation) than those of invention XVII, whose expression in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

28. Inventions VIII and XVIII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention VIII, drawn to a method of making a producer cell line comprising introducing the lentiviral vector of claim 1 into a host cell, wherein the lentiviral vector is a transfer plasmid, and introducing a packaging plasmid and an envelope plasmid into the host cell, is distinct from invention XVIII drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral particle. The methodologies require the use of distinct lentiviral vectors and the methodology of producing a stable cell line, such as that in invention VIII requires distinct steps and reagents and effect (such as cell selection via a selectable marker and host cell

propagation) than those of invention XVIII, whose lentiviral particle infection in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

29. Inventions VIII and XIX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention VIII, drawn to a method of making a producer cell line comprising introducing the lentiviral vector of claim 1 into a host cell, wherein the lentiviral vector is a transfer plasmid, and introducing a packaging plasmid and an envelope plasmid into the host cell, is distinct from invention XIX drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific

recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid. The methodologies require the use of distinct lentiviral vectors and the methodology of producing a stable cell line, such as that in invention VIII requires distinct steps and reagents and effect (such as cell selection via a selectable marker and host cell propagation) than those of invention XIX, whose lentiviral transfer plasmid in a mammal results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

30. Inventions VIII and XX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention VIII, drawn to a method of making a producer cell line comprising introducing the lentiviral vector of claim 1 into a host cell, wherein the lentiviral vector is a transfer plasmid, and introducing a packaging plasmid and an envelope plasmid into the host cell, is distinct from invention XX drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose

presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral particle. The methodologies require the use of distinct lentiviral vectors and the methodology of producing a stable cell line, such as that in invention VIII requires distinct steps and reagents and effect (such as cell selection via a selectable marker and host cell propagation) than those of invention XX, whose lentiviral particle infection in a mammal results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

31. Inventions VIII and XXI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention VIII, drawn to a method of making a producer

cell line comprising introducing the lentiviral vector of claim 1 into a host cell, wherein the lentiviral vector is a transfer plasmid, and introducing a packaging plasmid and an envelope plasmid into the host cell, is distinct from invention XXI drawn to a method of treating or preventing infection by an infectious agent, the method comprising the steps of: administering to a subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising an effective amount of a lentiviral vector, wherein presence of the lentiviral vector in a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that is targeting to a transcript produced during infection by the infectious agent, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspect of infection by or replication of the infectious agent. The methodologies require the use of distinct lentiviral vectors and the methodology of producing a stable cell line, such as that in invention VIII requires distinct steps and reagents and effect (such as cell selection via a selectable marker and host cell propagation) than those of invention XXI and the treatment of a subject for treating or preventing infection by an infectious agent, whose lentiviral particle infection in a mammal results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

32. Inventions VIII and XXII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use

together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention VIII, drawn to a method of making a producer cell line comprising introducing the lentiviral vector of claim 1 into a host cell, wherein the lentiviral vector is a transfer plasmid, and introducing a packaging plasmid and an envelope plasmid into the host cell, is distinct from invention XXII drawn to a method of treating or preventing a disease or clinical condition, the method comprising: removing a population of cells from a subject at risk of or suffering from a disease or clinical condition; engineering or manipulating the cells to contain an effective amount of siRNA or shRNA targeted to a transcript, which transcript is characterized in that its degradation delays, prevents or inhibits one or more aspects of the disease or clinical condition, and returning at least a portion of the cells to the subject. The methodologies require the use of distinct lentiviral vectors and the methodology of producing a stable cell line, such as that in invention VIII requires distinct steps and reagents and effect (such as cell selection via a selectable marker and host cell propagation) than those of invention XXII of treating or preventing a disease or clinical condition, whose process requires the removal of donor cells and transplantation of those cell back into the donor. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

33. Inventions IX and X are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention IX drawn to a method of producing lentiviral particles by introducing the lentiviral vector of claim 1 into a helper cell that expresses protein required for production of infectious lentiviral particles is distinct from invention X, drawn to a method of expressing a heterologous nucleic acid in a target cell comprising introducing a lentiviral vector of claim 1 into the target cell, wherein the lentiviral vector comprises a heterologous nucleic acid operably linked to a promoter, and expressing the heterologous nucleic acid therein. The method of producing lentiviral particles of invention IX uses distinct replication defective lentiviral vectors (hence requiring a helper cell) which are not required in the method of invention X. Additionally, the methodology of invention X does not require the use of a helper cell, and thus the lentiviral vectors are not necessarily replication defective and can be expressed and produced in any cell. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

34. Inventions IX and XI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect;

(2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention IX drawn to a method of producing lentiviral particles by introducing the lentiviral vector of claim 1 into a helper cell that expresses protein required for production of infectious lentiviral particles is distinct from invention XI drawn to a method for achieving controlled expression of a heterologous nucleic acid in a cell comprising the steps of: (i) providing a modified lentiviral vector comprising a heterologous nucleic acid inserted between sites for recombinant; (ii) introducing the modified lentiviral vector into the cell; and (iii) subsequently inducing expression of the recombinant in the cell, thereby preventing expression of the heterologous nucleic acid within the cell. The method of producing lentiviral particles of invention IX uses distinct replication defective lentiviral vectors (hence requiring a helper cell) which are not required in the method of invention XI. Additionally, the methodology of invention XI does not require the use of a helper cell, and thus the lentiviral vectors are not necessarily replication defective and can be expressed and produced in any cell. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

35. Inventions IX and XV are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the

inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention IX drawn to a method of producing lentiviral particles by introducing the lentiviral vector of claim 1 into a helper cell that expresses protein required for production of infectious lentiviral particles is distinct from invention XV drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral transfer plasmid. The method of producing lentiviral particles of invention IX uses distinct replication defective lentiviral vectors (those from claim 1 which are distinct from those of claim 74 that are used in invention XV) and the replication defective lentiviral vectors of invention IX (hence requiring a helper cell) are not required in the method of invention XV. Additionally, the methodology of invention XV does not require the use of a helper cell, and thus the lentiviral vectors are not necessarily replication defective and can be expressed and produced in any cell, and the result of the methodology is the inhibition of a target transcript, which is not required in invention IX. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

36. Inventions IX and XVI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant

case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention IX drawn to a method of producing lentiviral particles by introducing the lentiviral vector of claim 1 into a helper cell that expresses protein required for production of infectious lentiviral particles is distinct from invention XVI drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral particle. The method of producing lentiviral particles of invention IX uses distinct replication defective lentiviral vectors (those from claim 1 which are distinct from those of claim 74 that are used in invention XVI) and the replication defective lentiviral vectors of invention IX (hence requiring a helper cell) are not required in the method of invention XVI. Additionally, the methodology of invention XVI does not require the use of a helper cell, and thus the lentiviral particles are not necessarily replication defective and can be expressed and produced in any cell, and the result of the methodology is the inhibition of a target transcript, which is not required in invention IX. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

37. Inventions IX and XVII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect

and do not overlap in scope. Invention IX drawn to a method of producing lentiviral particles by introducing the lentiviral vector of claim 1 into a helper cell that expresses protein required for production of infectious lentiviral particles is distinct from invention XVII drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid. The method of invention IX does not require the use of a lentiviral plasmids that form a particular secondary structure in order to produce a helper cell line, nor the use of recombinase sites, and can be done without the use of the 3 plasmid system of invention XVII. Since the helper cell already exists in invention VI, it would not require the transformation of 3 plasmids, as the proteins required for viral replication would already by in side the cell, thus the methodology is distinct. Additionally, the methodology of invention XVII does not require the stable transformation of the host cell prior to transformation of the viral vector, and does not result in the production of viral particles. Furthermore, the inventions as claimed do not

encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

38. Inventions IX and XVIII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention IX drawn to a method of producing lentiviral particles by introducing the lentiviral vector of claim 1 into a helper cell that expresses protein required for production of infectious lentiviral particles is distinct from invention XVIII drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral particle. The method of invention IX does not require the use of a lentiviral plasmids that form a particular secondary structure in order to produce a helper cell line,

nor the use of recombinase sites, and can be done without the use of the 3 plasmid system of invention XVIII. Since the helper cell already exists in invention VII, it would not require the transformation of 3 plasmids, as the proteins required for viral replication would already be inside the cell, thus the methodologies are distinct. Additionally, the methodology of invention XVIII does not require the stable transformation of the host cell prior to transformation of the viral particle, and does not result in the production of viral particles, but in the inhibition of gene expression. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

39. Inventions IX and XIX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention IX drawn to a method of producing lentiviral particles by introducing the lentiviral vector of claim 1 into a helper cell that expresses protein required for production of infectious lentiviral particles is distinct from invention XIX drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA

that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid. The method of invention IX does not require the use of a lentiviral plasmids that form a particular secondary structure in order to produce a helper cell line, nor the use of recombinase sites, and can be done without the use of the 3 plasmid system of invention XIX. Since the helper cell already exists in invention VII, it would not require the transformation of 3 plasmids, as the proteins required for viral replication would already be inside the cell, and does not require expression in a mammal, thus the methodologies are distinct. Additionally, the methodology of invention XIX does not require the stable transformation of the host cell prior to transformation of the viral plasmid, and does not result in the production of viral particles, but in the inhibition of gene expression in a mammal. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

40. Inventions IX and XX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant

case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention IX drawn to a method of producing lentiviral particles by introducing the lentiviral vector of claim 1 into a helper cell that expresses protein required for production of infectious lentiviral particles is distinct from invention XX drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral particle. The method of invention IX does not require the use of a lentiviral particles that form a particular secondary structure in order to produce a helper cell line, nor the use of recombinase sites, and can be done without the use of the 3 plasmid system of invention XX. Since the helper cell already exists in invention VII, it would not require the transformation of 3 plasmids, as the proteins required for viral replication would already be inside the cell, and does not require expression in a mammal, thus the methodologies are distinct. Additionally, the methodology of invention XX does not require the stable transformation of the host cell prior to transformation of the viral plasmid, and does not result in the production of viral

particles, but in the inhibition of gene expression in a mammal. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

41. Inventions IX and XXI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention IX drawn to a method of producing lentiviral particles by introducing the lentiviral vector of claim 1 into a helper cell that expresses protein required for production of infectious lentiviral particles is distinct from invention XXI drawn to a method of treating or preventing infection by an infectious agent, the method comprising the steps of: administering to a subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising an effective amount of a lentiviral vector, wherein presence of the lentiviral vector in a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that is targeting to a transcript produced during infection by the infectious agent, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspect of infection by or replication of the infectious agent. The methodology of producing a lentiviral particle from a helper cell is distinct from treating a subject for an infection from an infectious agent. The protocols

would require different reagents (cell culture vs. gene therapy/vaccination reagents), methods (cell culture incubators vs. clinical standards), etc. The methodology of invention XXI treats the subject using a viral particle, but it is not required that the same viral particle of invention XXI be used to do so, as the viral particles produced in invention IX do not have the structural requirements of the viral particles of invention XXI. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

42. Inventions IX and XXII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention IX drawn to a method of producing lentiviral particles by introducing the lentiviral vector of claim 1 into a helper cell that expresses protein required for production of infectious lentiviral particles is distinct from invention XXII drawn to a method of treating or preventing a disease or clinical condition, the method comprising: removing a population of cells from a subject at risk of or suffering from a disease or clinical condition; engineering or manipulating the cells to contain an effective amount of siRNA or shRNA targeted to a transcript, which transcript is characterized in that its degradation delays, prevents or inhibits one or more aspects of the disease or clinical condition, and returning at least a portion of the cells to the

subject. The methodology of producing a lentiviral particle from a helper cell is distinct from treating a subject for an disease. The protocols would require different reagents (cell culture vs. gene therapy/vaccination reagents), methods (cell culture incubators vs. clinical standards), etc. The methodology of invention XXII treats the subject using a viral particle, but it is not required that the same viral particle of invention XXII be used to do so, as the viral particles produced in invention IX do not have the structural requirements of the viral particles of invention XXII. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

43. Inventions X and XI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention X drawn to a method of expressing a heterologous nucleic acid in a target cell comprising introducing a lentiviral vector of claim 1 into the target cell, wherein the lentiviral vector comprises a heterologous nucleic acid operably linked to a promoter, and expressing the heterologous nucleic acid therein is distinct from invention XI, drawn to a method for achieving controlled expression of a heterologous nucleic acid in a cell comprising the steps of: (i) providing a modified lentiviral vector comprising a heterologous nucleic acid inserted between sites for recombinant; (ii)

introducing the modified lentiviral vector into the cell; and (iii) subsequently inducing expression of the recombinant in the cell, thereby preventing expression of the heterologous nucleic acid within the cell. The method of expressing the nucleic acids in a cell of invention 1 does not require the controlled expression of invention XI, including the recombination methodology. The expression of invention X could occur without the nucleic acid recombination in the transformed cell, and can be a continuous expression of the nucleic acids. Additionally, the methodology of invention XI can be performed with alternate lentiviruses, other than those of claim 1, which may not have the structural requirements necessary for recombination. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

44. Inventions X and XV are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention X drawn to a method of expressing a heterologous nucleic acid in a target cell comprising introducing a lentiviral vector of claim 1 into the target cell, wherein the lentiviral vector comprises a heterologous nucleic acid operably linked to a promoter, and expressing the heterologous nucleic acid therein is distinct from invention XV, drawn to a method of inhibiting or reducing the

expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral transfer plasmid. The methodology of invention X does not require that the expressed nucleic acid inhibits the expression of a target gene. The nucleic acid of invention X could be a nucleic acid that expresses a gene that is not native to the cell that it is being expressed in. The methodology of invention XV requires that the expression of the nucleic acid results in the reduction of a target nucleic acid, and requires the use of a specific lentiviral vector of claim 74, which is distinct from the lentiviral vector required in invention XV, which requires the use of the lentiviral vector of claim 1. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

45. Inventions X and XVI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention X drawn to a method of expressing a heterologous nucleic acid in a target cell comprising introducing a lentiviral vector of claim 1 into the target cell, wherein the lentiviral vector comprises a heterologous nucleic acid operably linked to a promoter, and expressing the heterologous nucleic acid therein is distinct from invention XVI drawn to a method of inhibiting or reducing the

expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral particle. The methodology of invention X does not require that the expressed nucleic acid inhibits the expression of a target gene. The nucleic acid of invention X could be a nucleic acid that expresses a gene that is not native to the cell that it is being expressed in. The methodology of invention XVI requires that the expression of the nucleic acid results in the reduction of a target nucleic acid, and requires the use of a specific lentiviral vector of claim 74, which is distinct from the lentiviral vector required in invention XVI, which requires the use of the lentiviral vector of claim 1. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

46. Inventions X and XVII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention X drawn to a method of expressing a heterologous nucleic acid in a target cell comprising introducing a lentiviral vector of claim 1 into the target cell, wherein the lentiviral vector comprises a heterologous nucleic acid operably linked to a promoter, and expressing the heterologous nucleic acid therein is distinct from invention XVII drawn to a method of reversibly inhibiting or

reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid. The methodology of invention X does not require that the expressed nucleic acid inhibits the expression of a target gene. The nucleic acid of invention X could be a nucleic acid that expresses a gene that is not native to the cell that it is being expressed in. The methodology of invention XVII requires that the expression of the nucleic acid results in the reduction of a target nucleic acid, and can be performed without the use of the lentiviral vector of claim 1, as required by invention X. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

47. Inventions X and XVIII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant

case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention X drawn to a method of expressing a heterologous nucleic acid in a target cell comprising introducing a lentiviral vector of claim 1 into the target cell, wherein the lentiviral vector comprises a heterologous nucleic acid operably linked to a promoter, and expressing the heterologous nucleic acid therein is distinct from invention XVIII drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral particle. The methodology of invention X does not require that the expressed nucleic acid inhibits the expression of a target gene. The nucleic acid of invention X could be a nucleic acid that expresses a gene that is not native to the cell that it is being expressed in. The methodology of invention XVIII requires that the expression of the nucleic acid results in the reduction of a target nucleic acid, and can be performed without the use of the lentiviral vector of claim 1, as required by invention X. Furthermore, the inventions as claimed do not encompass

overlapping subject matter and there is nothing of record to show them to be obvious variants.

48. Inventions X and XIX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention X drawn to a method of expressing a heterologous nucleic acid in a target cell comprising introducing a lentiviral vector of claim 1 into the target cell, wherein the lentiviral vector comprises a heterologous nucleic acid operably linked to a promoter, and expressing the heterologous nucleic acid therein is distinct from invention XIX drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid. The

methodology of invention X does not require that the expressed nucleic acid inhibits the expression of a target gene, nor the treatment of a mammal. The nucleic acid of invention X could be a nucleic acid that expresses a gene that is not native to the cell that it is being expressed in. The methodology of invention XIX requires that the expression of the nucleic acid results in the reduction of a target nucleic acid in a mammal, and can be performed without the use of the lentiviral vector of claim 1, as required by invention X. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

49. Inventions X and XX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention X drawn to a method of expressing a heterologous nucleic acid in a target cell comprising introducing a lentiviral vector of claim 1 into the target cell, wherein the lentiviral vector comprises a heterologous nucleic acid operably linked to a promoter, and expressing the heterologous nucleic acid therein is distinct from invention XX drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell

results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral particle. The methodology of invention X does not require that the expressed nucleic acid inhibits the expression of a target gene, nor the treatment of a mammal. The nucleic acid of invention X could be a nucleic acid that expresses a gene that is not native to the cell that it is being expressed in. The methodology of invention XX requires that the expression of the nucleic acid results in the reduction of a target nucleic acid in a mammal, and can be performed without the use of the lentiviral vector of claim 1, as required by invention X. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

50. Inventions X and XXI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention X drawn to a method of expressing a

heterologous nucleic acid in a target cell comprising introducing a lentiviral vector of claim 1 into the target cell, wherein the lentiviral vector comprises a heterologous nucleic acid operably linked to a promoter, and expressing the heterologous nucleic acid therein is distinct from invention XXI drawn to a method of treating or preventing infection by an infectious agent, the method comprising the steps of: administering to a subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising an effective amount of a lentiviral vector, wherein presence of the lentiviral vector in a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that is targeting to a transcript produced during infection by the infectious agent, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspect of infection by or replication of the infectious agent. The methodology of invention X does not require that the expressed nucleic acid forms specific secondary structures, nor that its expression results in the inhibition of a target gene, nor the treatment of a subject with an infection. The nucleic acid of invention X could be a nucleic acid that expresses a gene that is not native to the cell that it is being expressed in, providing a gene that does not treat an infectious agent, such a s a null gene for gene therapy, or the over production of a gene for nucleic acid amplification for a probe. The methodology of invention XXI requires that the expression of the nucleic acid results in the reduction of a target nucleic acid in a mammal suffering from or potentially suffering from and infection, and can be performed without the use of the lentiviral vector of claim 1, as required by invention X. Furthermore, the inventions as claimed do

not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

51. Inventions X and XXII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention X drawn to a method of expressing a heterologous nucleic acid in a target cell comprising introducing a lentiviral vector of claim 1 into the target cell, wherein the lentiviral vector comprises a heterologous nucleic acid operably linked to a promoter, and expressing the heterologous nucleic acid therein is distinct from invention XXII drawn to a method of treating or preventing a disease or clinical condition, the method comprising: removing a population of cells from a subject at risk of or suffering from a disease or clinical condition; engineering or manipulating the cells to contain an effective amount of siRNA or shRNA targeted to a transcript, which transcript is characterized in that its degradation delays, prevents or inhibits one or more aspects of the disease or clinical condition, and returning at least a portion of the cells to the subject. The methodology of invention X does not require that the expressed nucleic acid expression results in the inhibition of a target gene, nor the treatment of a subject with disease or clinical condition. The nucleic acid of invention X could be a nucleic acid that expresses a gene that is not native to the cell that it is being

expressed in, providing a gene that does not treat an infectious agent, such a s a null gene for gene therapy, or the over production of a gene for nucleic acid amplification for a probe in a bacterial cell. The methodology of invention XXII requires that the expression of the nucleic acid results in the reduction of a target nucleic acid in a subject suffering from a disease, and can be performed without the use of the lentiviral vector of claim 1, as required by invention X. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

52. Inventions XI and XV are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XI drawn to a method for achieving controlled expression of a heterologous nucleic acid in a cell comprising the steps of: (i) providing a modified lentiviral vector comprising a heterologous nucleic acid inserted between sites for recombinant; (ii) introducing the modified lentiviral vector into the cell; and (iii) subsequently inducing expression of the recombinant in the cell, thereby preventing expression of the heterologous nucleic acid within the cell is distinct from invention XV, drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral

vector is a lentiviral transfer plasmid. The methodology of invention XI does not require that the expressed nucleic acid inhibits the expression of a target gene. The nucleic acid of invention XI could be a nucleic acid that expresses a gene that is not native to the cell that it is being expressed in. The methodology of invention XV requires that the expression of the nucleic acid results in the reduction of a target nucleic acid, and requires the use of a specific lentiviral vector of claim 74, which is distinct from the lentiviral vector required in invention XV, which does not require the use of the lentiviral vector of claim 74. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

53. Inventions XI and XVI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XI drawn to a method for achieving controlled expression of a heterologous nucleic acid in a cell comprising the steps of: (i) providing a modified lentiviral vector comprising a heterologous nucleic acid inserted between sites for recombinant; (ii) introducing the modified lentiviral vector into the cell; and (iii) subsequently inducing expression of the recombinant in the cell, thereby preventing expression of the heterologous nucleic acid within the cell is distinct from invention XVI,

drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral particle. The methodology of invention XI does not require that the expressed nucleic acid inhibits the expression of the target gene but could be through the controlled expression of a protein which disrupts expression of a gene (eg a dominant negative). The nucleic acid of invention XI could be a nucleic acid that expresses a gene that is not native to the cell that it is being expressed in. The methodology of invention XVI requires that the expression of the nucleic acid results in the reduction of a target nucleic acid, and requires the use of a specific lentiviral vector of claim 74, which is distinct from the lentiviral vector required in invention XV, which does not require the use of the lentiviral vector of claim 74. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

54. Inventions XI and XVII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XI drawn to a method for achieving controlled expression of a heterologous nucleic acid in a cell comprising the steps of: (i) providing a modified lentiviral vector comprising a heterologous nucleic acid inserted between

sites for recombinase; (ii) introducing the modified lentiviral vector into the cell; and (iii) subsequently inducing expression of the recombinant in the cell, thereby preventing expression of the heterologous nucleic acid within the cell is distinct from invention XVII, drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid. The methodology of invention XI does not require that the expressed nucleic acid inhibits the expression of a target gene, but could be through the controlled expression of a protein which disrupts expression of a gene (eg a dominant negative). The nucleic acid of invention XI could be a nucleic acid that expresses a gene that is not native to the cell that it is being expressed in. The methodology of invention XVII requires that the expression of the nucleic acid results in the reduction of a target nucleic acid through the hybridization of siRNAs produced from the lentiviral vector. Thus the target, reagents and effects of the methods are distinct. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

55. Inventions XI and XVIII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XI drawn to a method for achieving controlled expression of a heterologous nucleic acid in a cell comprising the steps of: (i) providing a modified lentiviral vector comprising a heterologous nucleic acid inserted between sites for recombinase; (ii) introducing the modified lentiviral vector into the cell; and (iii) subsequently inducing expression of the recombinant in the cell, thereby preventing expression of the heterologous nucleic acid within the cell is distinct from invention XVIII, drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral particle. The methodology of invention XI does not require that the expressed

nucleic acid inhibits the expression of a target gene, but could be through the controlled expression of a protein which disrupts expression of a gene (eg a dominant negative). The nucleic acid of invention XI could be a nucleic acid that expresses a gene that is not native to the cell that it is being expressed in. The methodology of invention XVIII requires that the expression of the nucleic acid results in the reduction of a target nucleic acid through the hybridization of SiRNAs produced from the lentiviral vector. Thus the target, reagents and effects of the methods are distinct. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

56. Inventions XI and XIX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XI drawn to a method for achieving controlled expression of a heterologous nucleic acid in a cell comprising the steps of: (i) providing a modified lentiviral vector comprising a heterologous nucleic acid inserted between sites for recombinase; (ii) introducing the modified lentiviral vector into the cell; and (iii) subsequently inducing expression of the recombinant in the cell, thereby preventing expression of the heterologous nucleic acid within the cell is distinct from invention XIX drawn to a method for reversibly inhibiting or reducing expression of a transcript in a

mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid. The method of treating a mammal with a lentiviral transfer plasmid, as required by invention XIX will have different reagents and protocols than those of invention XI, which is the expression of a nucleic acid in a cell. The methodology of invention XI can be performed on other cell types, such as bacterial cells, and does not require that the nucleic acid expressed directly results in the inhibition go the target gene, but can be through the over-expression of a dominant negative protein. Thus the target, reagents and effects of the methods are distinct. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

57. Inventions XI and XX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the

inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XI drawn to a method for achieving controlled expression of a heterologous nucleic acid in a cell comprising the steps of: (i) providing a modified lentiviral vector comprising a heterologous nucleic acid inserted between sites for recombinase; (ii) introducing the modified lentiviral vector into the cell; and (iii) subsequently inducing expression of the recombinant in the cell, thereby preventing expression of the heterologous nucleic acid within the cell is distinct from invention XX, drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral particle. The method of treating a mammal with a lentiviral particle, as required by invention XX will have different reagents and protocols than those of invention XI, which is the expression of a nucleic acid in a cell. The methodology of invention XI can be performed on other cell types, such as bacterial cells, and does not require that the nucleic acid expressed directly results in the

inhibition go the target gene, but can be through the over-expression of a dominant negative protein. Thus the target, reagents and effects of the methods are distinct. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

58. Inventions XI and XXI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XI drawn to a method for achieving controlled expression of a heterologous nucleic acid in a cell comprising the steps of: (i) providing a modified lentiviral vector comprising a heterologous nucleic acid inserted between sites for recombinase; (ii) introducing the modified lentiviral vector into the cell; and (iii) subsequently inducing expression of the recombinant in the cell, thereby preventing expression of the heterologous nucleic acid within the cell is distinct from invention XXI, to a method of treating or preventing infection by an infectious agent, the method comprising the steps of: administering to a subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising an effective amount of a lentiviral vector, wherein presence of the lentiviral vector in a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that is targeting to a transcript produced during infection by the

infectious agent, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspect of infection by or replication of the infectious agent. The method of treating a subject with or prior to an infection, as required by invention XXI will have different reagents and protocols than those of invention XI, which is the expression of a nucleic acid in a cell (clinical protocols, administration of the viral vector dosages, etc). The methodology of invention XI can be performed on other cell types, such as bacterial cells, and does not require that the nucleic acid expressed directly results in the inhibition go the target gene, but can be through the over-expression of a dominant negative protein. Thus the target, reagents and effects of the methods are distinct. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

59. Inventions XI and XXII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XI drawn to a method for achieving controlled expression of a heterologous nucleic acid in a cell comprising the steps of: (i) providing a modified lentiviral vector comprising a heterologous nucleic acid inserted between sites for recombinase; (ii) introducing the modified lentiviral vector into the cell; and (iii)

subsequently inducing expression of the recombinant in the cell, thereby preventing expression of the heterologous nucleic acid within the cell is distinct from invention XXII, drawn to a method of treating or preventing a disease or clinical condition, the method comprising: removing a population of cells from a subject at risk of or suffering from a disease or clinical condition; engineering or manipulating the cells to contain an effective amount of siRNA or shRNA targeted to a transcript, which transcript is characterized in that its degradation delays, prevents or inhibits one or more aspects of the disease or clinical condition, and returning at least a portion of the cells to the subject. The method of treating a subject with a disease or condition requiring the removal of donor cells from the subject, as required by invention XXI will have different reagents and protocols than those of invention XI, which is the expression of a nucleic acid in a cell (clinical protocols, administration of the viral vector dosages, etc). The methodology of invention XI can be performed on other cell types, such as bacterial cells, and does not require that the nucleic acid expressed directly results in the inhibition go the target gene, but can be through the over-expression of a dominant negative protein. Thus the target, reagents and effects of the methods are distinct. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

60. Inventions XV and XVI are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other

combinations (MPEP § 806.05(c)). Invention XV is drawn to a method using lentiviral transfer plasmid, and the method of invention XVI uses a lentiviral particle. In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because the lentiviral particle of invention XVI does not require the specific lentiviral transfer plasmid of invention XV, and invention XV can be transformed into a host cell without the viral particle of invention XVI.

61. The examiner has required restriction between combination and subcombination inventions. Where applicant elects a subcombination, and claims thereto are subsequently found allowable, any claim(s) depending from or otherwise requiring all the limitations of the allowable subcombination will be examined for patentability in accordance with 37 CFR 1.104. See MPEP § 821.04(a). Applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

62. Inventions XV and XVII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XV drawn to a method of inhibiting or reducing

the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral transfer plasmid is distinct from invention XVII, drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid. The method of invention XV requires the use of a specific lentiviral vector that is not required in invention XVII. Invention XVII also requires that the methodology for the inhibition of the gene results directly from the SiRNA formations of the expressed nucleic acid, a requirement not found in invention XV. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

63. Inventions XV and XVIII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant

case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XV drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral transfer plasmid is distinct from invention XVIII drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral particle. The method of invention XV requires the use of a specific lentiviral vector that is not required in invention XVIII. Invention XVIII also requires that the methodology for the inhibition of the gene results directly from the SiRNA formations of the expressed nucleic acid, a requirement not found in invention XV. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

64. Inventions XV and XIX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect;

(2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XV drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral transfer plasmid is distinct from invention XIX drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid. The method of treating a mammal, as required by invention XIX will have different reagents and protocols than those of invention XV, which is the expression of a nucleic acid in a cell (clinical protocols, administration of the viral vector dosages, etc). The methodology of invention XV can be performed on other cell types, such as bacterial cells, and does not require that the nucleic acid expressed directly results in the inhibition go the target gene, but can be through the over-expression of a dominant negative protein, a

requirement of invention XIX. Thus the target, reagents and effects of the methods are distinct. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

65. Inventions XV and XX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XV drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral transfer plasmid is distinct from invention XX drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral particle. The method of treating a

mammal, as required by invention XX will have different reagents and protocols than those of invention XV, which is the expression of a nucleic acid in a cell (clinical protocols, administration of the viral vector dosages, etc). The methodology of invention XV can be performed on other cell types, such as bacterial cells, and does not require that the nucleic acid expressed directly results in the inhibition go the target gene, but can be through the over-expression of a dominant negative protein, a requirement of invention XX. Thus the target, reagents and effects of the methods are distinct. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

66. Inventions XV and XXI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XV drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral transfer plasmid is distinct from invention XXI drawn to a method of treating or preventing infection by an infectious agent, the method comprising the steps of: administering to a subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising an effective amount of a lentiviral vector, wherein presence of

the lentiviral vector in a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that is targeting to a transcript produced during infection by the infectious agent, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspect of infection by or replication of the infectious agent. The method of treating a subject with an infection, as required by invention XXI will have different reagents and protocols than those of invention XV, which is the expression of a nucleic acid in a cell (clinical protocols, administration of the viral vector dosages, etc). The methodology of invention XV can be performed on other cell types, such as bacterial cells, and does not require that the nucleic acid expressed directly results in the inhibition go the target gene, but can be through the over-expression of a dominant negative protein, a requirement of invention XXI. Thus the target, reagents and effects of the methods are distinct. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

67. Inventions XVI and XVII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVI drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of

claim 74 to the cell, wherein the lentiviral vector is a lentiviral particle is distinct from invention XVII, drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid. The methods utilize different reagents, invention XVI utilizing a lentiviral particle, whereas invention XVII utilizes a transfer plasmid. Thus the methodology for the incorporation of the nucleic acids into the cells differ, as the method of using a lentiviral particle differs from the lentiviral transfer plasmid in terms of quantity and concentration, reagents, and transformation methods. Further the method of invention XVII requires that he expressed transfer plasmid expresses a nucleic acid that has specific structural requirements not found in invention XVI. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

68. Inventions XVI and XVIII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect;

(2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVI drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral particle is distinct from invention XVIII, drawn to drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral particle. The methods utilize different lentiviral particles (invention XVI requires those from claim 74, which are not required for invention XVIII). Further the method of invention XVIII requires that the lentiviral particle expresses a nucleic acid that has specific structural requirements not found in invention XVII. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

69. Inventions XVI and XIX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVI drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral particle is distinct from invention XIX, drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid. The methods utilize different lentiviral particles (invention XVI requires those from claim 74, which are not required for invention XIX). The methods utilize different reagents, invention XVI utilizing a lentiviral particle, whereas invention XIX utilizes a transfer plasmid. Thus the

methodology for the incorporation of the nucleic acids into the cells differ, as the method of using a lentiviral particle differs from the lentiviral transfer plasmid in terms of quantity and concentration, reagents, and transformation methods. Further the method of invention XIX requires that the lentiviral particle expresses a nucleic acid that has specific structural requirements not found in invention XVI. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

70. Inventions XVI and XX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVI drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral particle is distinct from invention XX drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase,

which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral particle. The methods utilize different lentiviral particles (invention XVI requires those from claim 74, which are not required for invention XX). Further the method of invention XX requires that the lentiviral particle expresses a nucleic acid that has specific structural requirements not found in invention XVII. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

71. Inventions XVI and XXI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVI drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of claim 74 to the cell, wherein the lentiviral vector is a lentiviral particle is distinct from invention XXI drawn to a method of treating or preventing infection by an infectious agent, the method comprising the steps of: administering to a subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising an effective amount of a lentiviral vector, wherein presence of

the lentiviral vector in a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that is targeting to a transcript produced during infection by the infectious agent, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspect of infection by or replication of the infectious agent. The method of treating a subject with an infection, as required by invention XXI will have different reagents and protocols than those of invention XVI, which is the expression of a nucleic acid in a cell (clinical protocols, administration of the viral vector dosages, etc). The methodology of invention XVI can be performed on other cell types, such as bacterial cells, and does not require that the nucleic acid expressed directly results in the inhibition go the target gene, but can be through the over-expression of a dominant negative protein, a requirement of invention XXI. Thus the target, reagents and effects of the methods are distinct. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

72. Inventions XVI and XXII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVI drawn to a method of inhibiting or reducing the expression of a target transcript in a cell comprising delivering the lentiviral vector of

claim 74 to the cell, wherein the lentiviral vector is a lentiviral particle is distinct from invention XXII drawn to a method of treating or preventing a disease or clinical condition, the method comprising: removing a population of cells from a subject at risk of or suffering from a disease or clinical condition; engineering or manipulating the cells to contain an effective amount of siRNA or shRNA targeted to a transcript, which transcript is characterized in that its degradation delays, prevents or inhibits one or more aspects of the disease or clinical condition, and returning at least a portion of the cells to the subject. The method of treating a subject with a disease, as required by invention XXII will have different reagents and protocols than those of invention XVI, which is the expression of a nucleic acid in a cell (clinical protocols, administration of the viral vector dosages, etc). The methodology of invention XVI can be performed on other cell types, such as bacterial cells, and does not require that the nucleic acid expressed directly results in the inhibition go the target gene, but can be through the over-expression of a dominant negative protein, a requirement of invention XXII. Thus the target, reagents and effects of the methods are distinct. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

73. Inventions XVII and XVIII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant

case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVII is drawn to drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid whereas invention XVIII is drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral particle. The methods are distinct in that they are performed by two distinct entities, one lentiviral transfer plasmid, and a lentiviral particle. The methods of

using a plasmid will have different reagents, steps than those methods of using a particle. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

74. Inventions XVII and XIX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVII is drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid which is distinct from invention XIX which is drawn to drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell

results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid. The method of treating a mammal with a plasmid is distinct from the method of treating a cell with a plasmid. An isolated cell can be transformed using different techniques and protocols that those for transformation a mammal. Additional considerations in terms of concentrations of dosages will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

75. Inventions XVII and XIX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVII is drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with

in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid which is distinct from invention XIX which is drawn to drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid. The method of treating a mammal with a viral plasmid is distinct from the method of treating a cell with a plasmid. An isolated cell can be transformed using different techniques and protocols that those for the transformation of a mammal. Additional considerations in terms of concentrations of dosages will also differ and need to be accounted for.

Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

76. Inventions XVII and XX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVII is drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid which is distinct from invention XX drawn to drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form

an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral particle. The method of treating a mammal with a viral particle is distinct from the method of treating a cell with a plasmid. An isolated cell can be transformed using different techniques and protocols that those for the infection of a mammal. Additional considerations in terms of concentrations of dosages will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

77. Inventions XVII and XXI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVII is drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to

each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid which is distinct from invention XXI drawn to a method of treating or preventing infection by an infectious agent, the method comprising the steps of: administering to a subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising an effective amount of a lentiviral vector, wherein presence of the lentiviral vector in a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that is targeting to a transcript produced during infection by the infectious agent, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspect of infection by or replication of the infectious agent. The method of treating a subject from infection is distinct from the method of treating a cell with a plasmid. An isolated cell can be transformed using different techniques and protocols that those for the transformation of a mammal. Additional considerations in terms of concentrations of dosages will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

78. Inventions XVII and XXII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVII is drawn to a method of reversibly inhibiting or reducing expression of a target transcript in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral transfer plasmid which is distinct from invention XXII drawn to a method of treating or preventing a disease or clinical condition, the method comprising: removing a population of cells from a subject at risk of or suffering from a disease or clinical condition; engineering or manipulating the cells to contain an effective amount of siRNA or shRNA targeted to a transcript, which transcript is characterized in that its degradation delays, prevents or inhibits one or more aspects of the disease or clinical condition, and returning at least a portion of the

cells to the subject. The method of treating a subject with a disease or clinical condition is distinct from the method of treating a cell with a plasmid. An isolated cell can be transformed using different techniques and protocols that those for the transformation of a diseased subject. Additional considerations in terms of concentrations of dosages will also differ and need to be accounted for and the method will vary depending on the type of disease. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

79. Inventions XVIII and XIX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVIII is drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least

one of the RNAs, wherein the lentiviral vector is a lentiviral particle which is distinct from the method of invention XIX drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid. The method of treating a mammal with a viral plasmid is distinct from the method of treating a cell with a viral particle. An isolated cell can be infected using different techniques and protocols that those for the transformation of a mammal. Additional considerations in terms of concentrations of dosages will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

80. Inventions XVIII and XX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant

case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVIII is drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral particle is distinct from invention XX, drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral particle. The method of treating a mammal with a viral particle is distinct from the method of treating a cell with a viral particle. An

isolated cell can be infected using different techniques and protocols that those for the infection of a mammal. Additional considerations in terms of concentrations of dosages will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

81. Inventions XVIII and XXI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVIII is drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral particle is distinct from invention XXI, drawn to a method of treating or preventing infection by an infectious

agent, the method comprising the steps of: administering to a subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising an effective amount of a lentiviral vector, wherein presence of the lentiviral vector in a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that is targeting to a transcript produced during infection by the infectious agent, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspect of infection by or replication of the infectious agent. The method of treating a subject suffering from or prior to infection with an infectious agent, with a viral vector is distinct from the method of treating a cell with a viral particle. An isolated cell can be infected using different techniques and protocols that those for the treatment for an infectious agent, and have different results. On the cellular level, the reduction of a transcript may be limited to that transcript, however the result of such reduction of transcription in a subject may have systemic results that are not possible to obtain or assess in an in vitro cell system. Additional considerations in terms of concentrations of dosages, type of infection etc will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

82. Inventions XVIII and XXII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the

inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XVIII is drawn to a method of reversibly inhibiting or reducing expression of a target transcription in a cell comprising the steps of: (i) delivering a lentiviral vector to the cell, wherein the presence of the lentiviral vector with in the cell results in synthesis of one or more RNAs that self-hybridize or hybridize to each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site specific recombinase, wherein nucleic acid segment provides a template for transcription of one the one or more RNAs; and (ii) inducing the expression of the site specific recombinase within the cell, thereby preventing synthesis of at least one of the RNAs, wherein the lentiviral vector is a lentiviral particle is distinct from invention XXII, drawn to a method of treating or preventing a disease or clinical condition, the method comprising: removing a population of cells from a subject at risk of or suffering from a disease or clinical condition; engineering or manipulating the cells to contain an effective amount of siRNA or shRNA targeted to a transcript, which transcript is characterized in that its degradation delays, prevents or inhibits one or more aspects of the disease or clinical condition, and returning at least a portion of the cells to the subject. The method of treating a subject suffering from a disease or medical condition, with a viral vector is distinct from the method of treating a cell with a viral particle. An isolated cell can be infected using different techniques and protocols that those for the treatment for any disease, and have different results. On the cellular

level, the reduction of a transcript may be limited to that transcript, however the result of such reduction of transcription in a subject may have systemic results that are not possible to obtain or assess in an in vitro cell system. Additional considerations in terms of concentrations of dosages, type of disease treated etc will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

83. Inventions XIX and XX are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XIX is drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at

least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid is distinct from invention XX, drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral particle. The method of treating a mammal with a viral plasmid is distinct from the method of treating a mammal with a viral particle. The transformation of in vivo cell with a plasmid require different reagents and protocols that those of the in vivo infection of a mammal with a viral particle. Additionally, the viral plasmid of invention XIX is not necessarily required to confer the functional requirements that the viral particle of XX provides, and can easily be provided by that viral particle of invention XX from alternate viral nucleic acids, such as those that are part of the viral particle's genome, and not from the recombinant transfer plasmid. Additional considerations in terms of concentrations of dosages will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

84. Inventions XIX and XXI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XIX is drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid is distinct from invention XXI drawn to a method of treating or preventing infection by an infectious agent, the method comprising the steps of: administering to a subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising an effective amount of a lentiviral vector, wherein presence of the lentiviral vector in a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA

that is targeting to a transcript produced during infection by the infectious agent, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspect of infection by or replication of the infectious agent. The method of reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner using the expression of siRNA is distinct from treating an infection in a subject. The method of treating as subject does not require that the treatment is cell or tissue specific, and does not require the treatment of a specific animal or cell. The method of treating a mammal to in a cell specific manner requires reagents and protocols to direct and control the expression of the transcript, using a lentiviral transfer plasmid, are requirements that are not found in invention XXI. Additional considerations in terms of concentrations of dosages will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

85. Inventions XIX and XXII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XIX is drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific

manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral transfer plasmid is distinct from invention XXII, drawn to a method of treating or preventing a disease or clinical condition, the method comprising: removing a population of cells from a subject at risk of or suffering from a disease or clinical condition; engineering or manipulating the cells to contain an effective amount of siRNA or shRNA targeted to a transcript, which transcript is characterized in that its degradation delays, prevents or inhibits one or more aspects of the disease or clinical condition, and returning at least a portion of the cells to the subject. The method of reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner using the expression of siRNA is distinct from treating an infection in a subject. The method of treating as subject does not require that the treatment is cell or tissue specific, and does not require the treatment of a specific animal or cell. The method of treating a mammal to in a cell specific manner requires reagents and protocols to direct and control the expression of the transcript, using a lentiviral transfer plasmid, are requirements that are not found in invention XXII.

Additional considerations in terms of concentrations of dosages will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

86. Inventions XX and XXI are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XX is drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral particle is distinct from invention XXI, drawn to a method of treating or preventing infection by an infectious agent, the method comprising the steps of: administering to a

subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising an effective amount of a lentiviral vector, wherein presence of the lentiviral vector in a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that is targeting to a transcript produced during infection by the infectious agent, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspect of infection by or replication of the infectious agent. The method of reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner using the expression of siRNA is distinct from treating an infection in a subject. The method of treating as subject does not require that the treatment is cell or tissue specific, and does not require the treatment of a specific animal or cell. The method of treating a mammal to in a cell specific manner requires reagents and protocols to direct and control the expression of the transcript, using a lentiviral transfer particle, are requirements that are not found in invention XXI. Additional considerations in terms of concentrations of dosages will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

87. Inventions XX and XXII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the

inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XX is drawn to a method for reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner comprising: (i) delivering to the mammal a lentiviral vector whose presence within a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that inhibits expression of the target transcript, wherein the lentiviral vector comprises a nucleic acid segment located between sites for a site-specific recombinase, which nucleic acid segment provides a template for transcription of the RNA; and (ii) inducing expression of the site specific recombinase in a subset of the cells of the animal, thereby preventing synthesis of at least one of the RNAs within the subset of cells, wherein the lentiviral vector is lentiviral particle is distinct from invention XXII, drawn to a method of treating or preventing a disease or clinical condition, the method comprising: removing a population of cells from a subject at risk of or suffering from a disease or clinical condition; engineering or manipulating the cells to contain an effective amount of siRNA or shRNA targeted to a transcript, which transcript is characterized in that its degradation delays, prevents or inhibits one or more aspects of the disease or clinical condition, and returning at least a portion of the cells to the subject. The method of reversibly inhibiting or reducing expression of a transcript in a mammal in a cell type or tissue-specific manner using the expression of siRNA is distinct from treating or preventing a disease in a subject. The method of treating as subject does not require that the treatment is cell or tissue

specific, and does not require the treatment of a specific animal or cell. The method of treating a mammal to in a cell specific manner requires reagents and protocols to direct and control the expression of the transcript, using a lentiviral transfer particle, are requirements that are not found in invention XXII. Additional considerations in terms of concentrations of dosages will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

88. Inventions XXI and XXII are directed to related methodologies. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, function and effect and do not overlap in scope. Invention XXI is drawn to a method of treating or preventing infection by an infectious agent, the method comprising the steps of: administering to a subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising an effective amount of a lentiviral vector, wherein presence of the lentiviral vector in a cell results in synthesis of one or more RNAs that self-hybridize or hybridize with each other to form an shRNA or siRNA that is targeting to a transcript produced during infection by the infectious agent, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspect of infection by or replication of the infectious agent is distinct

from invention XXII, drawn to a method of treating or preventing a disease or clinical condition, the method comprising: removing a population of cells from a subject at risk of or suffering from a disease or clinical condition; engineering or manipulating the cells to contain an effective amount of siRNA or shRNA targeted to a transcript, which transcript is characterized in that its degradation delays, prevents or inhibits one or more aspects of the disease or clinical condition, and returning at least a portion of the cells to the subject. The method of treating or preventing an infection from an infectious agent is different than treating or preventing any disease or clinical condition in a subject. The method of treating a disease or clinical condition requires step that are not requires in the method of treating an infection due to an infectious agent. Additionally the methods will have to be individually tailored to address the type of condition, disease state or infectious agent involved, and as such considerations in terms of concentrations of dosages, treatment regiments, subject being treated, will also differ and need to be accounted for. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

89. **Group I: Inventions I, II, III, IV, XII, and XIII are all directed towards distinct lentiviral compositions.**

Group II: Inventions V, VI and XIV are all directed towards distinct collections or libraries of lentiviral compositions or viruses.

90. Group III: Inventions VIII, IX, X, XI, XV, XVI, XVII, XVIII, XIX, XX, XXI and XXII are all directed towards distinct methodologies using lentiviral vectors.

91. **Group IV: Invention VII is drawn to a transgenic animal and methods of making the transgenic animal.**

92. Inventions of group I (individual lentiviral compositions) and group II (collections or libraries of lentiviral compositions or viruses) are directed to related inventions. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, and do not overlap in scope. The lentiviral compositions of group I are all distinct lentiviral vectors, comprising structural or functional requirements between the individual compositions, which is distinct from the collections of lentiviral compositions of group II. Group II, can be comprised to lentiviral compositions of group I, but is not limited to those compositions, and it is reasonable to expect that the collections comprise additional lentiviral compositions not disclosed in group I. Additionally, the lentiviral compositions of Group I do not have to be placed in a collection, but individually can be utilized for their own purposes, such as individual expression plasmids, or probes for immunoblots. There is no requirement that the lentiviral compositions of group I require a collection of more than 1 in order to function. Furthermore, the inventions as claimed do not

encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

93. Inventions of group I and group III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the lentiviral compositions of group I can be used in multiple alternative methodologies (as evidenced by the multiple methodologies within group III), but can also be used in alternative methodologies, such as the generation of a transgenic animal. Furthermore, the methodologies of group III can be performed using different lentiviral compositions than those of group I.

94. Inventions of group I and group IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the lentiviral compositions of group I can be used in multiple alternative methodologies other than the production of a transgenic animal (as evidenced by the multiple methodologies within group IV). Furthermore, the methodologies and transgenic animals of group IV can be performed using different lentiviral compositions than those of group I.

95. Inventions of group II and group III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the collections of lentiviral compositions of group II can be used in multiple alternative methodologies (as evidenced by the multiple methodologies within group III), but can also be used in alternative methodologies, such as bound to a microarray and screened for heterologous genes. Furthermore, the methodologies of group III can be performed using different lentiviral compositions than those of group II, and do not require the use of multiple lentiviral compositions in order to perform the methods.

96. Inventions of group II and group IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are not capable of use together and have different design. The transgenic animals of group IV do not comprise nor require a collection of lentiviral vectors for their generation.

97. Inventions of groups III and group IV are directed to an unrelated product and process. Product and process inventions are unrelated if it can be shown that the product cannot be used in, or made by, the process. See MPEP § 802.01 and § 806.06. In the instant case, the methodologies of invention III would not result in the generation of a transgenic animal.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

This application contains claims directed to the following patentably distinct species (A-E):

A) Claim 9 is generic to the following disclosed patentably distinct species: 4 distinct restrictions sites selected from Not1, ApaI, XhoI, XbaI, HPA,I, NheI, PacI, NsiI, SphI, Sma/Xma, AccI, BamHI, and SphI. The species are independent or distinct because each has a distinct nucleic acid recognition site. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

B) Claim 9 is generic to the following disclosed patentably distinct species: 5-13 distinct restrictions sites selected from Not1, ApaI, XhoI, XbaI, HPA,I, NheI, PacI, NsiI, SphI, Sma/Xma, AccI, BamHI, and SphI.

C) Claim 35 is generic to the following disclosed patentably distinct species: GFP, eGFP, dsRed, dsRed2, cyan fluorescent protein, yellow fluorescent protein, blue fluorescent protein, luciferase, and aequorin.

D) Claim 42 and 51 are generic to the following disclosed patentably distinct species: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9 Each nucleic acid represents a distinct sequence. The claim teaches the lentiviral vector comprising a single nucleic acid vectors. Applicant is required to select 1 nucleic acids sequence.

E) Claims 45 is generic to the following disclosed patentably distinct species: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9 Each nucleic acid represents a distinct sequence. The claim teaches the lentiviral vector comprising at least 2 of the nucleic acid vectors. Applicant is required to select up to 2 nucleic acids.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims

readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

98. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product

are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions

unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kam/07/30/07